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The Effect of Education on Age-Related Functional Activation During Working Memory

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ABSTRACT

Education has been suggested to play a protective role against the development of age-related dementias. Accordingly, we examined modulation of functional activation during working memory by age and education. Eight older individuals with a college education, six older individuals with a high school education, and eight younger individuals with a college education performed a working memory task during O^{15} [water] PET scanning. In a voxel-by-voxel whole brain search, older participants with less education demonstrated greater left frontal activation relative to older participants with more education. Older participants with more education demonstrated greater right precuneus activation relative to older participants with less education. This suggests that older less educated participants may have used additional frontal resources to compensate for dysfunctional parietal cortex. These results occurred in the context of similar activation in well-educated younger and older participants. Younger participants had one unique area of activation in the left posterior parietal cortex and no differences in frontal activation were observed between these two groups. The results of this study indicate the need to consider education in age-related neuroimaging studies.

As individuals age, changes occur in brain structure and function. Studies using structural imaging report age-related differences in volume throughout the brain, with the frontal lobes being particularly vulnerable (Raz et al., 1997). Age-related changes have been reported in the gray and white matter

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of the frontal lobes (Raz et al., 1997; Sullivan et al., 2001). Behavioral paradigms have also demonstrated deficits on frontal lobe tasks (e.g., Hedden & Park, 2001; Winocur, Moscovitch, & Stuss, 1996) and there are associations between decreased cognitive performance and the structural integrity of the frontal lobes in aging (Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002; O'Sullivan et al., 2001; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998). Recent advances in functional neuroimaging (positron emission tomography and functional magnetic resonance imaging) have enabled researchers to examine the brain in action. Using these techniques, researchers have observed differences in frontal activation between younger and older individuals on a variety of tasks (e.g., Cabeza et al., 1997; DiGirolamo et al., 2001; Esposito et al., 1999; Grady et al., 1994, 1995; Matty et al., 2002; Schrues et al., 2001; Stebbins et al., 2002).

That age-related changes in working memory are observed (e.g., Diagneault & Braun, 1993; Haut, Chen & Edwards, 1999) is not surprising given the relationship between the frontal lobes and working memory (Smith & Jonides, 1998). A number of studies have examined functional activation during the performance of working memory tasks and have noted age-related differences in frontal lobe activation (Grady et al., 1998; Grossman et al., 2002 Haut Kuwabara, Leach, & Callahan, 2000b; Reuter-Lorenz et al., 2000; Rypma, Prabhakaran, Desmond, & Gabrieli, 2001; Smith et al., 2001). Older individuals, relative to younger individuals, show less activation in the typical working memory areas within the frontal cortex and often demonstrate unique areas of activation within the frontal cortex. A number of studies have reported increased utilization of the left dorsolateral prefrontal cortex in older subjects, with a concurrent decrease in activation of the right dorsolateral prefrontal cortex (Grady et al., 1998; Haut et al., 2000b; Rypma et al., 2001). Other studies have reported the same laterality pattern in other prefrontal regions such as the inferior prefrontal cortex (Grossman et al., 2002). Additionally, one study observed that aging results in bilateral rather than unilateral frontal lobe activation during working memory (Reuter-Lorenz et al., 2000). Cabeza (2002) recently proposed the HAROLD (Hemispheric Asymmetry Reduction in Older Adults) model, which asserts that aging results in bilateral rather than unilateral patterns of activation. One interpretation of this model is that bilateral activation in aging represents the utilization of different brain regions to compensate for dysfunctional tissue.

One limitation of the existing aging and activation literature, as pointed out by Cabeza (2002), is that the vast majority of studies have used individuals with a high level of education. Level of education may alter the pattern of activation and thus may influence conclusions drawn from aging studies. For example, a recent study of young, healthy individuals reported that prefrontal cortex activation during working memory was related to intelligence (Gray, Chabris, & Braver, 2003). There is a well-established relationship between intelligence and education, although it is clear they are not perfect correlates. Recently, Scarmeas et al. (2003) examined the effect of education/intelligence on age-related activation. They used a combination of measures of education and estimated intelligence to create a summary score that represented cognitive reserve. They observed differences in activation in posterior brain regions during visual recognition memory as a function of reserve. However, no differences were observed in the frontal cortex.

The purpose of the present study was to examine the effect of education on age-related functional activation during working memory. Working memory was chosen because of the robust frontal activation typically observed with these tasks. Participants completed a working memory task and a control task while undergoing O^{15} [water] PET scanning. First, in what is a typical aging and activation study, younger participants with a college education were compared to older individuals with a college education. We hypothesized that older participants would have greater left frontal activation and younger participants would have greater right frontal activation. This hypothesis is consistent with the majority of age-related working memory activation studies reviewed above. Next, we compared a group of older individuals with a high school education to the group of older participants with a college education to examine the effect of education on activation. We hypothesized that the older participants with less education would show bilateral frontal activation compared to the older participants with more education, as the less-educated group is expected to require more resources to perform the task.

METHOD

Participants

Eight older individuals with a minimum of a college education (O+), six older individuals with a maximum of a high school education (O-), and eight younger individuals with a college education (Y) served as participants. Some of the younger individuals were included as part of a separate publication (Haut, Kuwabara, Leach, & Arias, 2000a). All participants were right-handed and completed a screening questionnaire to rule out medical (e.g., hypertension), psychiatric (e.g., depression), substance abuse, and neurological (e.g., head injury) conditions that could affect cognition and/or cerebral blood flow. No participant was taking or prescribed psychoactive medication at the time of the study. Older participants completed the Mini-Mental State Exam (MMSE; Folstein, Folstein & McHugh, 1975) to screen for cognitive impairment. All subjects scored 28 or higher. Participants also completed the word reading subtest of the Wide Range Achievement Test -3 (Wilkinson, 1993). Table 1 provides demographic information for the

TABLE 1. Demographic features of the sample

Group	Age	Education[a,b]	WRAT-3 Reading[a]
Young N=8	23.3(1.6)	16.4(0.9)	50.9(3.2)
Old+ N=8	67.3(10.4)	18.4(1.3)	53.1(2.6)
Old- N=6	72.1(7.2)	11.8(0.4)	42.0(11.5)

Age and education are reported in years. WRAT-3 reading is reported as the raw score. All scores are means, with standard deviation in parentheses.
[a] Old+ > Old-, p<.05
[b] Old+ > Young, p<.05

participants. As designed, O+ had significantly more education than O-, $F(1,12) = 141$, $p < .05$. In addition, O+ had significantly more years of education than Y, $F(1,14) = 12.6$, $p < .05$. For word reading ability, O+ was significantly greater than O-, $F(1,14) = 11.5$, $p < .05$, but O+ and Y were not reliably different, $F(1,12) = 2.3$, $p > .05$. O+ and O- did not differ significantly in age, $F < 1$.

Materials

During scanning, participants completed a version of the Number-Letter Sequencing subtest of the Wechsler Adult Intelligence and Memory Scales (Wechsler, 1997). In the Number-Letter Sequencing task, individuals listened to alternating numbers and letters and then repeated the numbers in ascending order, followed by the letters in alphabetical order. For example, 5-J-3-C-8 would be reported as 3-5-8-C-J. A span of 5 numbers and letters was used for each trial. As a control, subjects completed a Number-Letter Span task in which they listened to 5 numbers and letters and then repeated them aloud in the same order. Thus, 5-J-3-C-8 would be reported as 5-J-3-C-8. All trials in both span and sequencing tasks contained five items. Number of trials completed and percent of trials correctly completed were calculated for each task. Using subtraction methodology, the contrast between Number-Letter Sequencing and Number-Letter Span should yield the activation associated with manipulating the numbers and letters in working memory. We previously reported that the activation associated with this contrast in young, healthy subjects was typical for working memory activation studies including prefrontal and parietal cortex (Haut et al., 2000a).

Procedures

All participants signed a consent form approved by the Institutional Review Board of West Virginia University and the Radioactive Drug Research Committee of West Virginia University approved the study. Each subject had a venous catheter placed in his or her nondominant antecubital vein for injection of 20mCi of O^{15} [water] for each scan. A General Electric

PET camera was used in a 3D acquisition mode. Tissue radiation attenuation was measured by a 511-keV gamma source [^{68}GE] scan. Tasks began at the time of the injection and the scan was started after a sharp increase in the coincidence counts. The scanning period lasted 60 seconds. Participants performed the tasks for the entire scanning period. Subjects received a total of 6 scans: two Number-Letter Sequencing scans, two Number-Letter Span scans, and two scans not reported here. The order of scans was randomized. Participants had their eyes closed during all scans. PET data were reconstructed to tomographic images of 2.3mm x 2.3mm x 4.2mm voxels (35 slices), corrected for attenuation, random, and coincidence counts using software supplied by the manufacturer.

Analysis

PET image processing and subsequent statistical tests were performed using SPM2 (http://www.fil.ion.ucl.ac.uk) implemented in Matlab (Mathworks, Sherborn, Mass., USA). After between-scan movement correction, an average of all the scans for each participant was normalized to a standard PET template supplied by SPM2b. Then, individual PET volumes were directly transferred to the standard space by combining parameters of between-scan head movement correction and spatial normalization. Each volume was then smoothed by a Gaussian kernel (12 mm full-width at half-maximum, FWHM) and resliced to 2 mm^3 voxels. Mean whole brain cerebral blood flow was normalized (50m/100g/min) using proportional scaling. We examined the predetermined contrast of Number-Letter Sequencing vs. Number-Letter Span separately for each of the three groups using a voxel-by-voxel whole brain search for voxels (minimum of 10 contiguous) that exceeded the statistical threshold. The threshold was set at $p < .001$ uncorrected, and standardized z-scores were derived.

We then calculated interactions to examine the effect of age and education separately on activation during working memory. To examine age effects on the Number-Letter Sequencing vs. Number-Letter Span contrast, we compared Y and O+. A whole brain voxel-by-voxel search was conducted for active voxels (minimum of 10 contiguous) that exceeded the statistical threshold of $p < .001$, uncorrected, for the Y vs. O+ contrast. The procedure was then repeated for voxels for the O+ vs. Y contrast. To examine the effects of education on the Number-Letter Sequencing vs. Number-Letter Span contrast, we repeated the above procedures for O+ vs. O- and then O- vs. O+ contrast. For each of the whole brain searches described above, we used the average of the two repeated measurements for each condition to decrease the variance and noise. For each of the interaction analyses we report only those areas that survived the threshold and were present in the region of peaks that were observed when examining the contrast separately for each group. This is a more conservative approach than a comparison of activation between groups using a region of interest analysis or comparing activation between groups for the peaks obtained for each group individually (e.g., Haut et al., 2000b; Rypma & D'Esposito, 2000). A voxel-by-voxel examination of an interaction lessens the chance of reporting erroneous differences between groups that arise when a relative difference emerges between groups.

RESULTS

Behavioral Performance

Behavioral performance was examined with one-way ANOVAs comparing Y vs. O+ and O+ vs. O- separately. The mean number of trials completed during the 60-second scanning period and the percentage of those trials completed correctly are listed in Table 2. For Y vs. O+, there was no difference in the number of trials completed for Number-Letter Span, $F(1,14) < 1$, but Y completed significantly more trials than O+ on Number-Letter Sequencing, $F(1,14) = 18.3$, $p < .05$. The percentage of correct trials for Number-Letter Span, $F(1,14)=2.7$, $p>.05$ and Number-Letter Sequencing, $F(1,14)=2.3$, $p>.05$ did not differ between these groups. In comparing O+ with O-, there was no difference between groups in the number of trials completed for Number-Letter Span, $F(1,12) = 1.9$ $p>.05$, or Number Letter Sequencing, $F(1,12) = 2.1$ $p>.05$. There was no difference between these groups in the percentage of trials completed correctly for Number-Letter Span, $F(1,12)=2.1$, $p>.05$, or for Number-Letter Sequencing, $F(1,12) < 1$, $p>.05$.

PET Data

Main Effects

For Y, activation was observed in the frontal and parietal cortices bilaterally. For O+, activation was observed bilaterally in the parietal cortex and the right frontal cortex. For O-, activation was present in the right parietal cortex and left frontal cortex. Table 3 contains the peaks of activation for each group and Figure 1 displays those areas of activation.

TABLE 2. Behavioral Performance

Group	Total Trials Span Task	Total Trials Sequencing Task[a]	% Correct Span Task	% Correct Sequencing Task
Young	6.6 (.7)	5.4 (.6)	88 (16.9)	68 (23.8)
Old+	6.1 (1.1)	4.3 (.5)	73 (20.4)	48 (29.0)
Old-	5.3 (.9)	4.6 (.4)	53 (11.9)	43 (21.8)

Scores are reported as means with standard deviations in parentheses
[a] Young > Old+, p<.05

Interactions

The interactions of age and education for the contrast of Number-Letter Sequencing vs. Number-Letter Span are listed in Table 4 and highlighted in Figure 1. Y demonstrated greater activation than O+ in the left parietal cortex. O+ did not demonstrate any regions of greater activation than Y. When comparing older subjects, O+ demonstrated greater activation relative to O- in the right parietal cortex. O- demonstrated greater activation than O+ in the left frontal cortex.

DISCUSSION

The results of this study demonstrated functional activation in brain regions typical for working memory, prefrontal and parietal cortices, in each

TABLE 3. Activation Peaks for Number-Letter Sequencing vs. Number-Letter Span

Young	x	y	z	z score	Voxels	Brain Region
Left Hemisphere	-8	-76	54	4.28	247	PCu (BA 7)
	-38	-66	42	4.04	314	LPi (BA 40)
	-36	12	58	3.74	72	GFm (BA 6)
Right Hemisphere	34	-72	52	4.71	779	LPs (BA 7)
	34	18	54	3.84	132	GFm (BA 6)
	32	64	4	3.48	37	GFm (BA 10)
Older More Education	x	y	z	z score	Voxels	Brain Region
Left Hemisphere	-8	-74	54	3.42	43	PCu (BA 7)
	-40	-80	46	3.37	19	LPi (BA 40)
Right Hemisphere	12	-80	56	3.83	56	PCu (BA 7)
	48	28	36	3.21	34	GFm (BA 9)
	34	-68	38	3.32	27	LPi (BA 40)
Older Less Education	x	y	z	z score	Voxels	Brain Region
Left Hemisphere	-42	14	56	3.95	48	GFm (BA 6)
Right Hemisphere	42	-62	48	3.94	96	LPi (BA 40)

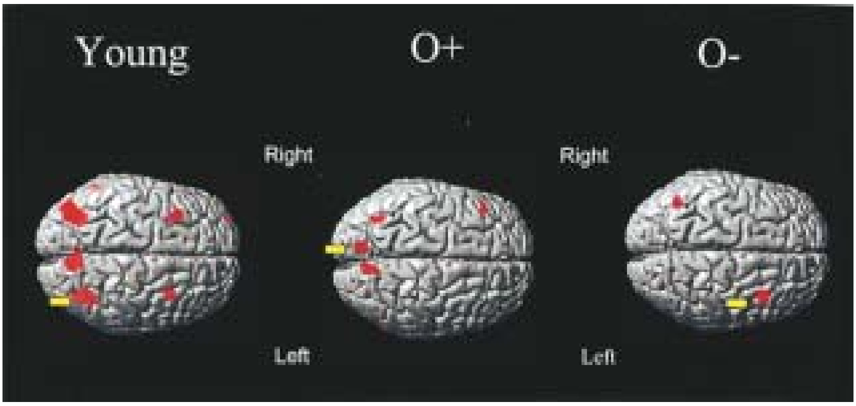
Coordinates (x, y, z) for each peak, z-value and location using Brodmann's areas (BA) for Number-Letter Sequencing vs. Number-Letter Span. GFm = middle frontal gyrus, LPi = inferior parietal lobule, LPs = superior parietal lobule, PCu = precuneus.

TABLE 4. Interactions of age and education

	x	y	z	z score	Voxels	Brain Region
Y > O+	-40	-38	36	3.39	90	LPi (BA 40)
O+ > O-	8	-80	42	4.06	50	PCu (BA 7)
O - > O+	-40	14	60	3.21	20	GFm (BA 6)

Coordinates (x, y, z) for each peak, z-value and location using Brodmann's areas (BA) for Number-Letter Sequencing vs. Number-Letter Span. LPi = inferior parietal lobule, PCu = precuneus, GFm=middle frontal gyrus.

FIGURE 1. For each group, brain regions that were active when contrasting Number-Letter Sequencing and Number-Letter Span. The yellow arrows highlight the regions that were significantly different between groups when examining the interactions of age and education.



of the groups. However, there were differences in activation between these groups. First, a difference in the pattern of activation in older participants as a function of education was demonstrated. Second, age-related differences in functional activation in healthy, well-educated participants were observed. The findings and their implications are discussed below.

This study demonstrated that the pattern of activation during working memory in older adults varied as a function of education, even though level of performance on the task was equivalent. Consistent with our hypothesis, differential frontal lobe activation was observed. Older participants with less education demonstrated left prefrontal cortex activation, while older participants with more education had a peak of activation in the right posterior premotor cortex. This latter area of activation was not different between the two groups, and was present in the older less-educated group at a lower threshold ($p < .005$). Activation in the older, educated group remained unilateral even at a lower threshold. Thus, bilateral frontal activation was suggested in older participants with fewer years of education. In his description of the HAROLD model, Cabeza (2002) details a number of ways in which asymmetry reduction may go undetected in functional imaging research due to the thresholds that are chosen. The present findings represent another pattern that may indicate relative bilateral activation in older participants, that in which group comparisons demonstrate a significant difference in frontal activation in one hemisphere, but no difference in the activation observed in the other hemisphere. This pattern of relative bilateral activation supports the HAROLD model (Cabeza, 2002), but only for the older participants with less education and not for the comparison of younger and older well-educated subjects. It appears that the older participants with less education may have recruited more frontal cortex to perform the task at the same level as their well-educated counter-parts. This increased frontal activation may be an example of functional compensation for the relative decrease in right parietal activation observed in comparison to older well-educated individuals. Alternatively, older subjects with more education may require less frontal activation (i.e., manipulation of the information) as they are able to rely on storage processes.

It is intriguing that bilateral frontal activation may only be present in the older individuals with less education. It may well be that the difference in activation between groups reflects a difference in brain reserve capacity or cognitive reserve (Satz, 1993; Stern, 2002). In other words, individuals with different levels of education may compensate differently for the changes that occur in the brain with age. Cognitive reserve is a complex theoretical construct and many factors have been described in the literature to represent reserve, including education, intelligence, and activity level. While the present study underscores the importance of education, it does not permit conclusions about what aspects of education may be critical. Such questions remain to be empirically examined. The addition of a group of younger individuals with less education would allow us to speak more directly to cognitive reserve.

It has been reported that functional activation varies in older individuals by task performance. For example, on a source memory task, Cabeza, Anderson, Locantore, and McIntosh (2002) observed bilateral frontal activation in older subjects with good performance and unilateral activation in subjects with poor performance. This finding was interpreted as supporting the HAROLD model and as evidence that high functioning older participants compensate for aging by recruiting different brain regions. Performance-related recruitment of additional brain regions has also been observed with episodic memory encoding (Rosen et al., 2002), but not working memory (Smith et al., 2001). Smith et al. observed increased left prefrontal activation in older participants and low-performing younger participants. We observed recruitment of additional brain regions in less-educated older adults, specifically in the left premotor cortex. Further investigation is needed to determine whether similar effects on functional activation are produced when grouping older individuals by behavioral performance and level of education.

We are not aware of a previous study examining the effect of education on functional activation during working memory in normal aging. Scarmeas et al. (2003) examined the effect of cognitive reserve, which included education and an estimate of intelligence, on age-related activation during a visual recognition memory task. Differences were reported in the right inferior temporal gyrus, right postcentral gyrus, cingulate and left cuneus. No differences were noted in frontal activation, but the frontal demands of the task may have been minimal. The peaks of activation for each group during task performance were not reported. Thus, the extent of frontal activation produced by this task is unclear.

Our results have implications for the rapidly expanding efforts that use functional imaging to understand how the aging brain works. A large volume of work in the last few years has examined the different patterns of activation during a variety of cognitive operations in young versus older individuals, including working memory (e.g., Grady et al., 1998; Jonides et al., 2000; Reuter-Lorenz et al., 2000; Rypma et al., 2001) and memory encoding/ retrieval (e.g., Cabeza et al., 1997; Madden et al., 1999; Stebbins et al., 2002). With few exceptions (Báckman et al., 1997; Haut et al., 2000b) these investigations have only included participants with a college education or greater. The results of the present study suggest that such findings may need to be interpreted judiciously as functional activation may be affected by level of education. At minimum, the results of prior studies on age-related differences in functional activation may not generalize to the entire aging population.

This study demonstrated similarities in the pattern of activation during working memory in well-educated older and younger participants, with one unique difference. Consistent with previous research, both groups demonstrated activation in areas typical for working memory tasks (Cabeza & Nyberg, 2000). The younger participants used bilateral posterior parietal cortex, bilateral premotor cortex, and right orbital frontal cortex. The older participants activated the bilateral posterior parietal cortex and the right dorsolateral prefrontal cortex. However, we did not confirm our hypothesis that the older participants would demonstrate a unique region of activation in the prefrontal cortex. This may have been the result of our conservative approach to the analysis of group differences. However, Grady et al. (1998) detected group differences in frontal activation using a similar voxel-by-voxel whole brain search. Our findings indicate that age-related frontal differences may not be robust for all tasks if a conservative approach is taken with the analysis.

Comparison of the well-educated groups revealed a difference in activation in parietal cortex, an area typically associated with the storage component of working memory (Jonides et al., 1998). Younger participants showed an increase in activation in the left posterior parietal cortex, suggesting relatively more reliance on information storage processes as compared to older well-educated participants. Recall that the older participants with more education also had an increase in the right parietal cortex relative to older less-educated participants. Most reports of differences in activation between younger and older groups have focused on the frontal cortex. However, as in the current study, differences in parietal activation have been reported with working memory tasks (Grossman et al., 2002; Haut et al., 2000b) and age-related gray matter loss has been observed in the parietal cortex (Raz et al., 1997). Thus, age-related differences outside of the frontal cortex warrant integration into current conceptualizations of aging. Again, inclusion of a group of younger individuals with less education may clarify the meaning of the differences in parietal activation among the three groups.

The present results are based on small samples and require replication. To address the small sample size we used repeated measurements and a conservative approach to identifying peaks of activation. However, some potential confounds and limitations remain. First, the level of education of the older and younger subjects differed. This difference is likely not meaningful, however, as both groups had at least a college education and had equivalent reading recognition skills, which suggests their estimated intelligence was similar (Johnstone et al., 1997). Second, an inherent challenge in age-related functional imaging research lies in choosing a task that balances performance accuracy with task difficulty across groups. In the present study, there were performance differences between the well-educated subjects. Younger participants completed 20% more trials than the older well-educated groups. While the difference in activation between these two groups remained after covarying percentage of trials performed correctly, covariance will not control for an inverse relationship between activation and performance (i.e., less activation with superior performance). The lack of significant differences on other behavioral measures may be due to small sample size. The groups may differ in their performance, with such differences affecting activation. For instance, it is possible that older participants had more difficulty maintaining information and thus manipulating it. Individuals with a larger span capacity will perform the task well and complete more trials, thus engaging in more cognitive processing in the scanning period. We attempted to minimize this possibility by using a span of five items for all trials. In addition, our individual subjects' responses suggest all were manipulating the items, although the older participants did so less accurately. Thus we believe that the observed differences in activation reflect recruitment of different brain regions based on age and education and not differential cognitive processing.

Our findings point to several potential directions for future research. Patterns of activation in younger and older individuals with a range of education should be examined using different working memory tasks and other cognitive operations, such as memory encoding and retrieval paradigms. Differences in age-related frontal activation during working memory need to be examined using education as a continuous variable, similar to the approach taken by Scarmeas et al. (2003). Replication of the present results using a measure of intelligence as well as education as a moderating variable may be useful. In addition, studies should investigate the factor(s) in education and intelligence that enable the brain to compensate. Finally, functional activation during working memory should be examined using different indicators of brain reserve in the elderly, such as risk factors for vascular disease.

In summary, this study demonstrated education-dependent differences in the pattern of functional activation observed during working memory in older, healthy adults. These differences, in conjunction with the difference between older well-educated individuals and a group of younger well-educated participants, suggest that how the aging brain compensates is a function of education. These findings indicate the need to consider education in future age-related neuroimaging studies. In addition, further investigation of the possible influence of brain reserve capacity and intelligence on normal age-related activation is needed.

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